REMARKS

Claims 68, 70-72, 75-80, 82-83, 85-109, and 111-122 are presently pending in the case. Previously withdrawn claims 97-107 and 112-114 are now cancelled. Claims 1-67, 69, 73-74, 81, 84, and 110 were previously cancelled. Claims 123-126 have been added and are supported throughout the specification. Claims 123 and 124 are supported, for example, in claims 68 and 70. Claims 125 and 126 are supported, for example on page 54, lines 19-20. No new matter has been added.

Withdrawal of rejections

Applicant thanks the Examiner for the withdrawn rejections.

Rejection under 35 U.S.C. §103

Claims 68, 70-72, 75-80, 82-83, 85-86, 91-92, 95-96, and 108-111 are rejected under 35 U.S.C. §103(a) over Nemoto et al (JP 03-240729, hereinafter Nemoto) in view of Bhardwaj et al. (US 5,578,316, hereinafter Bhardwaj) and Melia et al (*Ailment. Pharmacol. Therap.* (1989) 3, 513-525, hereinafter Melia).

Claims 87-90, 93-94, and 115-120 are rejected for alleged obviousness over Nemoto in view of Bhardwaj, Melia, and Penkler (US 5,854,226, hereinafter Penkler).

Claims 121-122 are rejected for alleged obviousness over Nemoto in view of Bhardwaj, Melia, and Olinger (US 5,651,316, hereinafter Olinger).

For brevity, the rejections will be considered together.

> The Office Action characterizes the invention as a quick release pharmaceutical composition for oral administration comprising a[n]... active substance which has a solubility of at the most 0.1% w/v in 0.1N hydrochloric acid at room temperature... wherein... the particulate composition... [has] a mean particle size of at the most 250 micrometers, or at least 50% w/w of the particles will pass through a 180 micrometer sieve.. the active substance in contact with an alkaline substance; and.... when tested in ... 0.07N

hydrochloric acid… releases at least 50% w/w of the active substance within the first 20 minutes of the test.

The Office Action further asserts that Nemoto teaches "an oral solid preparation containing one or more types of antacids that accelerates the absorption of oxicam anti-inflammatory drugs….. and that granules of the antacid and oxicam anti-inflammatory drugs are disclosed." Nemoto is stated to be deficient in teachings regarding a mean particle size of the most 250 micrometers of the granules.

This deficiency is alleged to be overcome by the teachings of Bhardwaj who teaches a chewable pharmaceutical composition for oral administration wherein the final particle size is from about 200 to about 400 microns.

The motivation to combine the reference is alleged to be provided by Melia which allegedly teaches that the particle size is a characteristic that influences dissolution from tablets and capsules. The Office Action specifically cites page 515 of Melia which states "increasing the available surface area by reducing the particle size can often markedly improve dissolution rates and lead to dramatic improvement in bioavailability."

The Penkler reference is relied upon for allegedly teaching a pharmaceutical composition for oral administration comprising an inclusion complex of an NSAID including lornoxicam, an alkaline earth metal bicarbonate, and further active ingredients.

Olinger is relied upon to teach desirable crushing strength of chewable tablets.

The claims of the instant invention are drawn to compositions including particulate granules of a specific size. Nemoto teaches compositions including particulate granules of a specific size. Bhardwaj teaches compositions including particulate granules of a specific size. Melia does not teach compositions of particulate granules of a specific size. Melia teaches particulate active pharmaceutical ingredient (API), *i.e.*, drug of a specific size.

The text immediately following that cited by the Examiner on page 515 of Melia reads as follows:

> The classical example is the antifungal agent griseofluvin, which when originally used in clinical trials, was of mean particle diameter 10 µM and had an effective dose of 250 mg. Subsequently, it was found that reducing the particle size to 2.7µM enabled the oral dose to be halved and a correlation between the amount of drug absorbed and the drug surface area was demonstrated. A particle size of 5 µM or less is now specified for griseofluvin to be used in tablets.

It is clear from reading the entire passage, Melia is concerned with API particle size, not with granule particle size. The particle sizes cited by Melia are far too small to be granules. The Office Action noted the teachings of Klioze for allegedly teaching granules of 149 µm to 840 µm, which is more than an order of magnitude larger than the size particles taught by Melia, which clearly refers to API and not granules.

The first paragraph of Melia clearly distinguishes the disintegration of the tablet from the dissolution of the drug, noting that drug dissolution is substantially a property of the drug. Specifically, Melia states:

> In the previous review we described how the ***disintegration of a tablet or capsule*** is a relatively rapid process and it is controlled principally by the disintegrant within the dosage form. In contrast, the ***dissolution of the drug particles is usually much slower and, because it is primarily an intrinsic property of the drug solid itself***, it is generally more difficult to control.

Therefore, Melia can be understood to teach that selection of the disintegrant is a matter of choice which is not substantially relevant to dissolution rate of the API which is a property intrinsic to the drug itself. The only teachings in Melia in relation to granulation is a cautionary statement that granulation can change the crystal form of some drugs, therefore, careful control is required (see page 517, first paragraph). There is no teaching or suggestion regarding how granulation should be performed, or even if it should be performed as undesirable drug transformations can occur.

Melia cannot be understood to provide teachings regarding the desirability of reducing particle size of granules. Melia is concerned with particle size of API. Therefore, Melia can provide no reason to use the granulate particle size taught by Bhardwaj in the teachings of Nemoto.

Bhardwaj teaches a specific particle size to provide a chewable tablet that is palatable and is crushed by the teeth while chewing. Specifically, Bhardwaj states:

> One of the advantages of the coated drug particles of this invention is that they provide ***a method for formulating extremely palatable solid dosage units which contain unpleasant tasting drugs***. For example, orally administrable dosage units such as chewable tablets, troches, lozenges or sprinkle formulations may be prepared from the coated granules of this invention. The granules of the present invention are particularly suitable for use in preparing chewable tablets. (col. 3, lines 43-51)

There can be no teaching or motivation to provide the formulation of Nemoto as a chewable tablet. Bhardwaj teaches situations in which it would be advantageous to make a chewable tablet, which would not provide one with motivation to make the formulation of Nemoto into a chewable tablet. Specifically Bhardwaj states:

> Cimetidine is known to be one of many medicaments to have a pronounced bitter taste. ***This is not usually a problem when the dosage form employed is a capsule or a tablet designed to be swallowed, thereafter to disintegrate upon reaching the stomach.*** However, such dosage forms can be impractical when it is desired to administer a large amount of active ingredient, or to co-administer a relatively bulky second active ingredient such as an antacid or alginate. (col. 1, lines 28-34)

The formulation of Nemoto would be provided as a capsule or tablet for disintegration in the stomach that need not be administered in a large amount. There would be no motivation to modify the teachings of Nemoto to provide a chewable tablet. If there were motivation to combine Nemoto and Bhardwaj alone, this would have been delineated in the Office Action. However, the rejections set forth in the instant Office

Action including Melia demonstrate that there can be no motivation to combine the teachings of Nemoto and Bhardwaj alone.

The issue of obviousness in chemical cases has been reviewed by the Courts in view of the recent KSR decision.

> "While the KSR Court rejected a rigid application of the . . . TSM test in an obviousness inquiry, the Court acknowledged the importance of identifying '***a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination***."
>
> "***When there is a design need or market pressure to solve a problem*** and there is a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 127 S. Ct. at 1732. * * * That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound." *Takeda Chemical Industries Ltd. v. Alphapharm Pty*. 492 F.3d 1350 (Fed. Cir. 2007) [emphasis added]

The *KSR* decision does not abrogate the need for some suggestion in the reference or in the art to modify a particular reference in a particular manner. As noted in the TC1600 teaching examples for determining obviousness in view of KSR, "The Examiner is still required to provide a reasoned statement of the rejection grounded in the Graham inquiries. He or she must articulate a reason or rationale to support the obviousness rejection." [slide 2, emphasis in original]

Applicant submits that one of skill in the art would not recognize particle size as a "result effective variable" to solve any problem alleged by the Office Action to be provided by the teachings of Nemoto. To make a rejection for obviousness, a particular parameter must first be recognized as a result-effective variable, *i.e.*, a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said

variable might be characterized as routine experimentation *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). Although Bhardwaj may be considered to demonstrate that modification of granule size results in an improved chewable tablet, there can be no motivation to make a chewable tablet based on the teachings of Nemoto. There can be no motivation from the teachings of Bhardwaj to think that the NSAIDs of Nemoto are not amenable to administration in a non-chewable tablet or are to be administered in such bulk that a chewable formulation would be desirable. This lack of motivation is supported by the inclusion of Melia in the rejection to support the combination of the teachings of Nemoto and Bhardwaj as there can be no motivation to combine the two references alone. As noted above, Melia teaches the advantages of modifying the size of the API, not of the granules. In fact, Melia teaches that the specifics of the desintegrant has little to do with the dissolution of the API as discussed above. Melia can provide no motivation to modify granulation size. Neither Penkler nor Olinger provide anything to remedy the deficiencies of the combination of cited references.

Applicant submits that no reference has been provided by the Examiner to demonstrate that one of skill in the art would recognize particle size as a "result effective variable" for improved dissolution. Applicant acknowledges that the claims are drawn to compositions; therefore, the specific advantage provided by the combination does not need to be the reason for the combination of the references. However, there can be no motivation to prepare the formulation of Nemoto as a chewable tablet. This is clear from the teachings of Nemoto which describes the use of tablets to be swallowed whole, provides the preparations in hard capsules, and tests solubility in artificial gastric juice.

The MPEP section 2143.01 states:

> A statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made'" ***because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a prima facie case of obviousness***

> ***without some objective reason to combine the teachings of the references***. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). **"">[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396 quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006).

Applicant submits that there can be no motivation to combine the teachings of the references cited by the Examiner in the instant rejections as they are drawn to the importance of the size of two discrete classes of compositions, granules which are a combination of API and carriers, and API alone.

Further, reference is made to the teachings of Nemoto that variations of the formulations can alter the ability of granules to tablet properly (see page 3 of Nemoto). However, it is respectfully submitted that it would not be obvious that varying a parameter such as granule size would provide tablets with the appropriate hardness. The alleged teachings of desirable hardness of tablets by Ollinger provides no expectation that modification of the granule size would provide a tablet of the desired hardness.

Lastly, newly added claims 123 and 124 recite that at least 50% w/w of the particles of the particulate composition used in the manufacture of the composition pass through a 180 micrometer sieve. Newly added claims 125 and 126 recite that the particles of the particulate composition comprises a granulate. The newly added claims cannot be obvious in view of the cited art for at least the reasons set forth above.

Accordingly, reconsideration and withdrawal of the rejections under 35 USC §103(a) are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, Applicant believes the pending application is in condition for allowance.

FEE AUTHORIZATION

It is believed that no fee is due with this response. However, if a fee is due, the Commissioner is hereby authorized to charge any fee or credit any overpayment to the Deposit Account 04-1105 referencing the Docket No. 55682CON(71432).

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